antagonists are intended to minimize tissue damage in the absence of adequate blood supply. Quite a few drugs in this general category are considered promising, and several have been evaluated in clinical trials. Three drugs that block the glutamate receptors were tested in trials that were prematurely terminated when interim analyses indicated there would be no possibility of efficacy and drug-related adverse events occurred. All glutamate antagonists tested in clinical trials have varying side effects, including psychotic reactions and adverse cardiovascular actions. Thus, the doses of these drugs were lowered in the clinical trials to the point at which they were reasonably safe, but it appears that this strategy resulted in the loss of efficacy.

Other drugs that have neuroprotective properties have been tested. These include a free radical scavenger, a white cell antagonist, a GABA agonist, and several drugs that do not have well-defined mechanisms of action in ischemia. Currently no neuroprotective drug has been proven to be effective for acute stroke management.

This is an exciting time in the field of acute stroke therapy. After many years of frustration and failure, we are beginning to treat stroke as a medical emergency. Future clinical trials of other drugs should be facilitated by the demonstrated need to treat stroke patients rapidly. The requirement for urgent delivery of treatment without a thorough preceding diagnostic evaluation makes uncomfortable many physicians who were accustomed to the more deliberate pace of the past. We can now deliver treatments, however, that have an important impact on functional damage. This should be a source of realistic hope for stroke victims and of satisfaction for their physicians.

JUSTIN A. ZIVIN MD, PHD
La Jolla, California

REFERENCES

The Multicenter Acute Stroke Trial—Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. N Engl J Med 1996; 335:145–150

The National Institute of Neurological Disorders and Stroke—rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333:1581–1587

Zivin JA. Neuroprotective therapies in stroke. Drugs 1997; 54:83–89

New Approaches to Therapy of Amyotrophic Lateral Sclerosis

AMYOTROPHIC LATERAL SCLEROSIS (ALS) is a progressive and fatal disease involving degeneration of motor neurons in the spinal cord, brain stem, and cortex. Most patients with ALS die within three to four years of diagnosis, although some live substantially longer. Approximately 10% of ALS patients appear to have a familial form of the disease, but the clinical course and pathology of sporadic and familial cases is very similar. The precise cause of ALS is still unknown, but abundant new evidence supports several theories, including genetic factors, glutamate excitotoxicity, oxidative stress, and possibly diminished neurotrophic factors.

Glutamate is the primary excitatory neurotransmitter in the brain. Glutamate levels are elevated in serum, spinal fluid, and brain tissue of patients with ALS. There is also reduced clearance of glutamate from critical motor control areas in the central nervous system and reduced glutamate transfer protein. The preclinical effects of both riluzole and gabapentin in models of glutamate excitotoxicity and in the transgenic mouse model of motor neuron disease are encouraging. In organotypic cultures of spinal cord motor neurons that model glutamate excitotoxicity, riluzole and gabapentin produced significant neuroprotection. Both drugs prolonged survival in the transgenic mouse model with mutant superoxide dismutase, one of the animal models most closely mimicking ALS. In two randomized controlled clinical trials, riluzole, which inhibits glutamate release, prolonged survival in patients with ALS, albeit to a modest degree (for several months). Riluzole is now the only FDA-approved, disease-specific treatment for ALS. Gabapentin appeared to slow the inexorable weakness in a controlled clinical trial, but the results were not conclusive and a definitive trial is underway. Taken together, these results provide strong support for the role of glutamate excitotoxicity in the propagation of ALS.

The familial form of ALS is generally inherited in an autosomal dominant fashion; in approximately 20% of these patients, there is a mutation in the copper/zinc superoxide dismutase gene (SOD-1). Emerging evidence suggests that the buildup of free radicals plays an important role in pathogenesis. Administration of vitamin E delayed the onset of ALS in the transgenic mouse model, suggesting that oxidative stress may be important in disease initiation. Antioxidants may be helpful for patients, but more studies are needed to confirm their role.

Other therapeutic approaches to ALS involve neurotrophic factors. Preclinical studies with both ciliary neurotrophic factor and brain-derived neurotrophic factor (BDNF) were particularly promising, but large multicenter controlled trials of subcutaneous administration produced no beneficial effect upon the disease. Promising studies with intrathecal BDNF and glial-derived neurotrophic factor (GDNF) are underway. Finally, encouraging results from the US trial of Insulin-like growth factor (IGF-1), which show that the decline of function and quality of life for patients with ALS is slowing, are currently under review at the FDA.

Thus, for the first time, there are new, rational approaches to finding treatments for ALS based on a rapidly expanding body of experimental evidence about its pathogenesis. In many ways, ALS has become a prototype for neurodegenerative diseases.

Nonetheless, the mainstay of management is symptomatic treatment. Many options have all helped to alleviate the enormous burden of this disease: percutaneous endoscopic gastrostomy to attenuate weight loss in patients with swallowing difficulty, noninvasive mechanical ventilation to improve airway integrity and sleep, new lightweight mobility aids, and better medication for spasticity, depression, emotional incontinence, and cramps. A North

American ALS patient database, launched about two years ago, promises to provide new outcome data that should further raise the standard of care.

ROBERT G. MILLER, MD
San Francisco, California

REFERENCES

Gurney ME, Curring FB, Zhai P, Doble A, Taylor CP, Andrus PK, et al. Benefit of vitamin E, riluzole, and gabapentin in a transgenic model of familial amyotrophic lateral sclerosis. Ann Neurol 1996; 39:147–157

Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V, Miller RG, and the Amyotrophic Lateral Sclerosis/Riluzole Study Group II. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Lancet 1996; 347:1425–1431

Lai EC, Felice KJ, Festoff BW, Gawel MJ, Gelinas DF, Kratz R, et al. Effect of recombinant human insulin-life growth factor-1 on progression of ALS: a placebo-controlled study. Neurology 1997; 49:1621–1630

Miller RG, Moore D, Young LA, Armon C, Barohn RJ, Bromberg MB, et al. Placebo-controlled trial of gabapentin in patients with amyotrophic lateral sclerosis. Neurology 1996; 47:1383–1388

Status Epilepticus

STATUS EPILEPTICUS IS characterized by abnormally prolonged seizure activity. Although there are numerous forms of status epilepticus that parallel, in part, the various types of isolated seizures, this epitome is directed toward generalized convulsive status epilepticus (GCSE) in adults and older children. GCSE includes the most common forms of status epilepticus (generalized, tonic-clonic, and myoclonic) and is associated with relatively high levels of morbidity and mortality. Because a variety of studies suggest that the typical, isolated tonic-clonic seizure in adults lasts no more that 3 to 4 minutes, an operational definition can emphasize the time at which therapy for status epilepticus should be initiated. GCSE can be defined as at least *five* minutes of either continuous seizures or two or more discrete seizures between which there is incomplete consciousness recovery. This definition does not refer to a mechanism that defines the transition from an isolated seizure to status epilepticus. Recent experimental observations, however, indicate that potentially important molecular "switches" occur in neurotransmitter receptors within this general time frame and may have a critical role in causing the enhanced neuronal excitability that characterizes status epilepticus.

A comprehensive, community-based prospective study of status epilepticus from Richmond, Virginia, suggests that the frequency of cases of status epilepticus in the US is approximately 100,000 to 150,000 per year, roughly twice as high as previously thought. This study has also verified a number of previous conclusions regarding the prime importance of etiology and age as determinants of outcome in status epilepticus. Patients with GCSE from etiologies having a chronic or remote basis (such as refractory epilepsy, discontinuation of antiepileptic drugs, or chronic ethanol abuse) generally respond well to treatment and recover. In contrast, patients with GCSE induced by more acute processes (such as metabolic abnormalities, infection, stroke, head trauma, or drug toxicity) often have seizures that are resistant to typical, front-line therapy and are associated with a substantially higher morbidity and mortality. Also, patients older than 60 are significantly more prone to complications related to GCSE.

Two recent advances have been made in the initial treatment of patients with GCSE. Intravenous lorazepam has supplanted intravenous diazepam as the most commonly used first-line drug therapy. Although lorazepam and diazepam have similar efficacy in aborting GCSE, the preference for lorazepam stems from the recognition that it has a significantly longer duration of antiseizure effect (12 to 24 hours for lorazepam compared to 15 to 30 minutes for diazepam). The other new aspect of initial therapy concerns the recent availability of fosphenytoin (Cerebyx). Fosphenytoin is a water-soluble pro-drug of phenytoin that is converted to phenytoin by nonspecific phosphatases. The water-solubility allows fosphenytoin to be combined with any intravenous fluid (as opposed to phenytoin, which precipitates when mixed with glucose-containing solutions). Fosphenytoin can also be infused faster (150 mg per minute of phenytoin equivalents) than phenytoin (50 mg per minute). The time to reach therapeutic serum levels of phenytoin is approximately the same for both drugs when using the suggested infusion rates. Theoretically, the lack of propylene glycol as a diluent for fosphenytoin suggests there should be fewer hypotensive or adverse cardiac effects compared to intravenous phenytoin. Other than a lower rate of infusion site reactions with fosphenytoin, however, no differences between the two drugs in frequency or scope of adverse events have been shown thus far.

Refractory status epilepticus refers to a situation in which patients do not respond to front-line therapy with lorazepam and phenytoin (or fosphenytoin) followed by loading doses of phenobarbital. Patients with refractory status epilepticus usually need to be managed in an intensive care unit, and they require careful neurological assessment, including regular monitoring with electroencephalography. Until recently, barbiturate coma was the preferred treatment for refractory status epilepticus, despite the recognition that this form of therapy was associated with a high frequency of complications, most notably hypotension. Intravenous midazolam and propofol have recently become popular alternatives to phenobarbital; these drugs appear to have a substantially lower incidence of complications.

DANIEL H. LOWENSTEIN, MD
San Francisco, California

ACKNOWLEDGMENT

This work is supported by NIH grant RO1 31403.

REFERENCES

DeLorenzo R, Pellock J, Towne A, Boggs J. Epidemiology of status epilepticus. J Clin Neurophys 1995; 12:316–325

Kapur J, Macdonald R. Rapid seizure-induced reduction of benzodiazepine and Zn^{2+} sensitivity of hippocampal dentate granule cell $GABA_A$ receptors. J Neurosci 1997; 17:7532–7540

Stecker MM, Kramer TH, Raps EC, O'Meeghan R, Dulaney E, Skaar DJ. Treatment of refractory status epilepticus with propofol: clinical and pharmacokinetic findings. Epilepsia 1998; 39:18–26